DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS

27 APR 2016

MEMORANDUM FOR SGVT
ATTN: CAPT ANDREW O PAULUS

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Evaluation of Total Daily Dose and Glycemic Control for Patients Taking U-500 Insulin Admitted to the Hospital** presented at/published to **Journal Endocrine Practice** with MDWI 41-108, and has been assigned local file #**16173.**

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are 59 MDW staff member, we can forward your request for funds to the designated wing POC.

4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

DEPARTMENT OF THE AIR FORCE
AIR EDUCATION AND TRAINING COMMAND

19 April 2016

MEMORANDUM FOR 59 MDW
ATTN: CAPT ANDREW O. PAULUS

FROM: 502 ISG/JA

SUBJECT: Ethics Review for Publication Approval Request (Paulus)

1. Capt Paulus submitted a request for a legal review of his manuscript titled "Evaluation of Total Daily Dose and Glycemic Control for Patients taking U-500 Regular Insulin Admitted to the Hospital." There are no apparent conflicts of interests and the manuscript includes the required disclaimer. This manuscript may be presented for publication to the Journal of Endocrine Practice.

2. FACTS: Capt Paulus submitted the manuscript titled "Evaluation of Total Daily Dose and Glycemic Control for Patients taking U-500 Regular Insulin Admitted to the Hospital" for legal review. The author plans to submit the manuscript for publication to the Journal of Endocrine Practice.

3. LAWS AND REGULATIONS: DoD 5500.07-R, Joint Ethics Regulation (JER), section 3-305 lays out rules governing "Teaching, Speaking and Writing." If the subject of the writing "deals in significant part with any ongoing or announced policy, program or operation" of the Air Force, the author is required to include a disclaimer that states the "views presented are those of the speaker or author and do not necessarily represent the views of DoD or its Components."

4. ANALYSIS: The manuscript does not "deal in significant part with any ongoing or announced policy, program or operation" of the Air Force, however, the author and co-authors' affiliation with the military will be included as part of the manuscript. Therefore, the authors have included the required disclaimer that the views presented are those of the authors and do not necessarily represent the views of DoD or its Components. Although the disclaimer language included in the manuscript is not verbatim from the JER, the language used is appropriate and clearly captures the intent of the language used in the JER. A Public Affairs review will be needed if it has not already been obtained. There are no apparent conflicts of interest that would prohibit publication of this material.

5. CONCLUSIONS: The manuscript submitted for review included the disclaimer required by the JER. There are no conflicts of interest.

6. If you have any questions, please call me at 210-671-5771.

VERNISHA N. FOSTER, Capt, USAF
Assistant Staff Judge Advocate

I concur.

ARLENE R. CHRISTILLES
Chief, Civil Law

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

TO:	FROM: *(Author's Name/Rank/Grade/Office Symbol)*	PROTOCOL NUMBER:
Clinical Research	Andrew O. Paulus/Capt/O-3/SGVT GME/GHSE Student: ☒YES ☐NO	BAMC C.2014.152d

PROTOCOL TITLE – ***[NOTE: For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.]***
Evaluation of Total Daily Dose and Glycemic Control for Patients taking U-500 Insulin Admitted to the Hospital

1. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:
Evaluation of Total Daily Dose and Glycemic Control for Patients taking U-500 Insulin Admitted to the Hospital

2. FUNDING RECEIVED FOR THIS STUDY? ☐YES ☒NO FUNDING SOURCE:
DO YOU NEED FUNDING SUPPORT FOR PUBLICATION PURPO NO $90 / typeset page

3. IS THIS MATERIAL CLASSIFIED? ☐YES ☒NO

4. IS THIS MATERIAL SUBJECT TO ANY LEGAL RESTRICTIONS FOR PUBLICATION OR PRESENTATION THROUGH A COLLABORATIVE RESEARCH AND DEVELPMENT AGREEMENT (CRADA), MATERIAL TRANSFER AGREEMENT (MTA), INTELLECTUAL PROERTY RIGHTS AGREEMENT, ETC.?
☐YES ☒NO (NOTE: If the answer is 'YES' then attach a copy of the Agreement to the Publications/Presentations Request Form)

5. MATERIAL IS FOR *(Check appropriate box or boxes for approval with this request.)*:
(ATTACH COPY OF MATERIAL TO BE PUBLISHED/PRESENTED) ☒DOMESTIC RELEASE ☐FOREIGN RELEASE

☒	PUBLICATION/JOURNAL *(List intended publication/journal)* Endocrine Practice
☐	PUBLISHED ABSTRACT *(List intended journal)*
☐	POSTER *(To be demonstrated at meeting/Name of Meeting, City, State, and Date of Meeting)*
☐	PLATFORM PRESENTATION *(At civilian institutions/Name of Meeting, State, and Date of Meeting)*
☐	OTHER *(Describe; Name of Meeting, City, State, and Date of Meeting)*

6. ALL PUBLICATIONS/PRESENTATIONS NEED TO BE PLACED INTO THE DEFENSE TECHNICAL INFORMATION CENTER (DTIC) EFFECTIVE 1 JAN 2016 WHAT IS YOUR EXPECTED DATE WHEN YOU WILL NEED THE CRD TO SUBMIT YOUR CLEARED PRESENTATION/PUBLICATION TO DTIC?
1 Jan 2017

POINT OF CONTACT

7. WHO IS THE PRIMARY 59 MDW POINT OF CONTACT? *(Last, First, M.I.) (Include email)*	DUTY PHONE/PAGER No.
Paulus, Andrew O., andrew.paulus@us.af.mil	210-916-2829/594-2934

AUTHORSHIP AND CO-AUTHOR(S) *(List in the order they will appear in the manuscript)*

LAST NAME, FIRST NAME AND MI.	GRADE/RANK	SQUADRON/GROUP/OFFICE SYM	INSTITUTION *(If not 59*
a. *Primary/corresponding author* Paulus, Andrew O.	Capt/ O-3	959 CSPS/SGVT	
b.Colburn, Jeffrey	Maj/O-4	959 MDOS/SGOSE	
c.True, Mark W.	Col/O-6	959 MDOS/SGOSE	
d.Folaron, Irene	Lt Col / O-5	959 MDOS/SGOSE	
e.Graybill, Sky	MAJ/ O-4	MCHE-MDE	
g.Wardian, Jana	Civ/Ctr	59 MDSP/SGME	

I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401_IP AND 59 MDWI 41-103. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.

AUTHOR'S PRINTED NAME/RANK/GRADE	AUTHOR'S SIGNATURE	DATE
Paulus, Andrew O./ Capt/ O-3		04/14/2016
APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE	APPROVING AUTHORITY'S SIGNATURE	DATE
True, Mark W. / Col/ O-6 / Program Director, Endo Fellowship	Mark W True, M.D.	04/14/2016

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1st ENDORSEMENT *(SGVU Use Only)*

TO: Clinical Research Division 59 MDW/SGVU (Contact 292-7141 for email instructions)	1. DATE RECEIVED 4/15/2016	2 ASSIGNED PROCESSING REQUEST FILE NUMBER 16173
3. DATE REVIEWED: 15 April 2016	4. DATE FORWARDED TO 502 ISG/JAC:	

5 AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES: ☐NO ☐YES (If yes, give date) _____ ☐N/A

6. COMMENTS ☒APPROVED ☐DISAPPROVED

Wrong form used

PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	SIGNATURE OF REVIEWER	DATE
COL LINDA STEEL-GOODWIN, USAF	STEEL.GOODWIN.LINDA.1186463583	15 Apr 2016

2ND ENDORSEMENT *(502 ISG/JAC Use Only)*

TO: 502 ISG/JAC	1. DATE RECEIVED	2. DATE FORWARDED TO 59 MDW/PA

3. COMMENTS ☒APPROVED (In compliance with security and policy review directives) ☐DISAPPROVED

PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	SIGNATURE OF REVIEWER	DATE
Arlene R Christilles GS-14 Chief, Civ / Law		20 Apr 16

3RD ENDORSEMENT *(PA Use Only)*

TO: 59 MDW OFFICE OF PUBLIC AFFAIRS (PA)	1. DATE RECEIVED	2. DATE FORWARDED TO 59 MDW/SGVU

3. COMMENTS ☑ APPROVED (In compliance with security and policy review directives) ☐DISAPPROVED

21 April 2016 26 April 2016

PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	SIGNATURE OF REVIEWER	DATE
Christopher Carwile, TSgt/E-6, NCOIC, PA	CARWILE.CHRISTOPHER.STEWART.1280477229	26 April 2016

4TH ENDORSEMENT *(SGVU Use Only)*

TO: 59 MDW/SGVU	1. DATE RECEIVED

2. SENIOR AUTHOR NOTIFIED BY PHONE OF APPROVAL OR DISAPPROVAL

☐YES ☐NO ☐COULD NOT BE REACHED ☐LEFT MESSAGE

3. DATE WRITTEN NOTICE OF APPROVAL AND CLEARANCE MAILED TO AUTHOR:

4. COMMENTS ☐APPROVED ☐DISAPPROVED

PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	SIGNATURE OF REVIEWER	DATE

DEPARTMENT OF THE ARMY
BROOKE ARMY MEDICAL CENTER
3851 ROGER BROOKE DR.
FORT SAM HOUSTON, TX 78234

REPLY TO
ATTENTION OF:

MCHE-CI

November 26, 2014

MEMORANDUM FOR:	Capt Andrew Paulus, MC, USAF
FROM:	Brooke Army Medical Center (BAMC) Institutional Review Board
PROJECT TITLE:	[404539-1] Evaluation of Total Daily Dose and Glycemic Control for Patients on U-500R Admitted to the Hospital
REFERENCE #:	C.2014.152d
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	November 26, 2014
EXPIRATION DATE:	November 26, 2015
REVIEW TYPE:	Expedited Review

1. Congratulations! The Brooke Army Medical Center (BAMC) Institutional Review Board (IRB) reviewed and APPROVED your aforementioned protocol and supporting documents on November 26, 2014. The research is judged to constitute Minimal Risk. Your protocol was reviewed for regulatory compliance under Expedited Review, in accordance with 32CFR§219.110(b)(1) Federal Register Category [5]. Applicable OHRP (under 45CFR§46) and HIPAA (45CFR§160 and 164) regulations were also consulted.The protocol has been assigned control number C.2014.152d. Please refer to this designation in all correspondence.

2. This submission has received Expedited Review based on the applicable federal regulation.

a. The protocol is approved to include cases occurring between to1 July 2009 through 1 July 2014.

b. A waiver of informed consent has been approved IAW 32 CFR§219.116(d) for the entire study.

c. A HIPAA waiver has been submitted and approved.

d. No funding is requested from the Department of Clinical Investigation.

3. All documents labeled "*FINAL" within the Designer Page and Board Documents sections of IRBNet are to be utilized throughout the course of the study.

4. A Research Monitor is not required; protocol is no greater than minimal risk.

5. You are required to report all unanticipated problems involving risks to subjects or others (UPIRSOs) and Serious Adverse Events (SAEs) to the IRB. Any unanticipated adverse events must be reported to

the Human Protection Administrator within 24 hours by phone at (210) 916-2598 or (210) 916-0606 or by email at BAMC_IRB_AE@amedd.army.mil.

6. Protocol C.2014.152d will automatically terminate on November 26, 2015. If you plan to continue beyond this date, the required continuing review progress report is due to the BAMC IRB no later than six (6) weeks prior to the expiration date. The IRB will attempt to assist you by sending a reminder; however, submission of the continuing review report is your responsibility. Failure to submit the report on time will result in the expiration of your protocol and a requirement to cease all research activities until the entire protocol can be resubmitted.

7. Please be sure to maintain all records in accordance with the terms set forth in your protocol. You are required to have all records, including informed consent and HIPAA documents, available for review by the IRB or other federal agencies.

8. Any changes to your protocol, including any changes in personnel, may not be made without prior IRB approval. Please forward a request for any changes, along with their rationale, to the BAMC IRB for review and approval.

9. Please inform the IRB when the protocol is completed or changes status and forward any significant findings.

10. Please ensure that you remain in compliance with BAMC Memo 70-1. Review and approval of abstract and/or manuscript submissions should be made through the Department of Clinical Investigation prior to any release. Contact Ms. Ileana King-Letzkus at (210) 916-2000 for additional details.

11. If at any time you have questions regarding your responsibilities as a Principal Investigator, please contact Wendy Ching at 210-916-8227 or wendy.ching.civ@mail.mil. On behalf of the entire IRB, we wish you much success with your research protocol. We look forward to reviewing the progress of your study in the coming months.

This document has been electronically signed in accordance with all applicable regulations, and a copy is retained within our records.

Title Page

Title: Evaluation of Total Daily Dose and Glycemic Control for Patients taking U-500 Regular Insulin Admitted to the Hospital
Running Title: Inpatient Insulin in U-500 Patients

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Key Words: U-500 regular insulin, inpatient diabetes mellitus, insulin resistance

Conflict of Interest Statements/Financial Disclosures:
None of the authors have any conflicts of interest or financial disclosures.

The views expressed in this manuscript are those of the authors and do not represent official views of the US Air Force, Department of Defense, or US government.

Abstract

Objective: Patients using U-500 regular insulin are severely insulin resistant requiring high doses of insulin. It has been observed that a patient's insulin requirements may dramatically decrease after hospitalization. This study sought to systemically investigate this phenomenon.

Methods: We performed a retrospective chart review of patients with U-500 insulin outpatient regimens who were admitted to the San Antonio Military Medical Center over a five-year period. Each patient's outpatient total daily dose (TDD) of insulin was compared to the average inpatient TDD. The outpatient estimated average glucose (eAG) was calculated from the HgbA1c and compared to the average inpatient glucose.

Results: There were 27 patients with a total of 62 separate admissions. The average age was 64.4 years with a mean body mass index of 38.9 kg/m2 and eAG of 203mg/dl (HgbA1c of 8.7%). All patients were converted from U-500 to U-100 upon admission. The average inpatient TDD of insulin was 91 units vs. 337 units as outpatients ($p < 0.001$). Overall, 89% of patients received ≤ 50% of their outpatient TDD. The average inpatient glucose was slightly higher than the outpatient eAG, 234 mg/dl vs. 203 mg/dl ($p = 0.003$).

Conclusion: U-500 insulin is prone to errors in the hospital setting, so conversion to U-100 insulin is a preferred option. Despite a significant reduction in insulin TDD, these patients had clinically similar glucose levels. Therefore, patients taking U-500 insulin as an outpatient can be converted to a U-100 basal-bolus regimen at 25 to 50% of their home TDD upon hospitalization.

Introduction

U-500 regular insulin is five times more concentrated than U-100 regular insulin and is generally used in patients with severe insulin resistance requiring greater than 200 units of insulin per day (1). It was first introduced as concentrated bovine U-500 insulin in 1952 by Eli Lilly and subsequently replaced by porcine U-500 insulin in 1980. The current formulation of U-500 human insulin (Humalin R U-500) was introduced in 1997 and is currently the only formulation available (2, 3). The number of patients treated with U-500 insulin has significantly increased in recent years as shown by a 97% increase in prescriptions written between August 2008 and September 2010. The increase mirrors the epidemics of obesity and type 2 diabetes mellitus (2, 3). These severely insulin resistant patients require high doses of insulin to achieve glycemic control.

With the rise in U-500 insulin use, the number of patients taking this medication who are admitted to hospitals has also increased. The use of U-500 insulin in the hospital has created some challenges to effective care. There are no formal published guidelines on inpatient management for patients treated with U-500 insulin. The literature is sparse on how outpatient U-500 insulin regimens should be managed during hospitalization. Concentrated U-500 insulin is considered a high alert medication for use in hospitals (4). The American Society of Health-System Pharmacist and the Institute for Safe Medication Practices (ISMP) have strict recommendations regarding U-500 insulin use in the hospital and some recommend against its routine use in the inpatient setting even in patients being prescribed U-500 insulin as an outpatient (1, 5).

Use of U-500 insulin in the inpatient setting is prone to errors at every step of the prescribing, storing, dispensing and administration process (4, 5). Some hospitals do not carry U-500 on formulary or have policies against its use (6). Lack of a U-500 calibrated syringe is a large source of confusion among both patients and physicians. U-500 insulin is either prescribed as units on a U-100 insulin syringe or milliliters

hospital days that patients spent the entire 24 hour period from midnight to midnight in the hospital. Partial days like the day of admission and the day of discharge were not included because the total daily dose of insulin and glucose values could not be accurately determined. The type of insulin (long versus short acting) was not distinguished, only the total amount of insulin given. The average daily glucose was calculated from the point of care glucose levels recorded in the medical chart. The admitting team decided what insulin regimen to start as there was no standardized insulin protocol for U-500 insulin patients at our institution.

Each patient's outpatient TDD of insulin was compared to the average inpatient TDD. The patient's outpatient estimated average glucose (eAG) was calculated from the HgbA1c and compared to the average inpatient glucose level during their admission. Statistical Package for the Social Sciences (SPSS) 19 software was used to analyze the data. A paired t-test was used to compare outpatient versus inpatient TDD of insulin and outpatient versus inpatient glucose.

Results

There were 75 patients admitted to the hospital that were prescribed U-500 insulin at some point during the study's five-year timeframe. Of those, 48 patients were not included in our analysis for the following reasons: 28 patients were not using a U-500 insulin regimen at the time of their admission, 15 patients had stays less than 24 hours, and five patients had undeterminable outpatient insulin doses. Thus, data were collected on 27 patients with a total of 62 separate admissions (Table 1). There were eight female and 19 male patients. The mean age was 64.4 years with a mean body mass index (BMI) of 38.9 kg/m^2 and mean eAG of 203mg/dL [74 – 109] (HgbA1c of 8.7% [4.6 – 5.6]). The mean length of stay was four days.

All patients were converted from U-500 to various U-100 insulin regimens upon admission to include insulin drip, basal bolus regimen, or sliding scale only regimen. Three patients received at least one dose

of U-500 during their stay, and it appeared from the chart review they were switched to a U-100 insulin regimen because of difficulty in obtaining U-500 insulin on the inpatient service. There was no protocol or standardized conversion for these patients, so their inpatient insulin regimen was determined by the admitting teams' preference.

The average inpatient TDD of insulin was 91 units, significantly lower than the average outpatient TDD of 337 units ($p < 0.001$), representing 27% of the outpatient insulin dose. The median values were lower with an inpatient TDD of 65 units and outpatient TDD of 270 units, but with a similar reduction of insulin received at 24.1% of the outpatient dose. Overall, 89% of patients received ≤ 50% of their outpatient TDD while in the hospital. The average inpatient glucose was slightly higher than the outpatient eAG, 234 mg/dL vs. 203 mg/dL ($p = 0.003$). Figure 1 shows the change in the TDD of insulin over the course of the first five days of hospitalization. The percent of home TDD started out at 100% when the patient was an outpatient and dropped to 24.5% on the first day of admission. As the insulin was titrated, it peaked at 36.2% of home TDD on day four and decreased to 29.2% on day five. During this time, the patient's average glucose increased from the outpatient eAG of 203 mg/dL to 242.5 mg/dL on day one and gradually decreased as the insulin was titrated up and was 195.8 mg/dL on day five.

Data was collected on a total of 245 hospital days. The average glucose was less than 180 mg/dL on 86 (35.1%) of those days. During those days, patients received an average of 30.0% of their home TDD of insulin. Finally, there was no difference in the amount of insulin received based on the patients' level of glycemic control prior to admission. Patients with a HgA1c less than 8% required 29% of their home TDD while patients with a HbA1c greater than or equal to 8% required a similar 27% of their TDD.

Discussion

The use of U-500 regular insulin has increased in recent years due to a rise in severe insulin resistance defined as requiring greater than 200 units of insulin per day (2, 3). When patients taking U-500 insulin

on a tuberculin syringe (5). The ISMP recommends U-500 insulin vials never be stored on the hospital floor and stored separately from other insulins in the pharmacy to avoid accidental use (4, 5). The pharmacokinetics of U-500 insulin includes both a bolus effect and a basal effect with a duration of action of 11.5 hours (4). This places hospitalized patients at risk for hypoglycemia because they frequently miss meals for test and procedures. This has led some physicians to recommend against routine use of U-500 insulin in the inpatient setting even on patient's prescribed U-500 insulin as an outpatient (1). If U-500 insulin is to be used during a hospitalization, it has been recommended that it be prescribed by a multidisciplinary team with multilayered safeguards to prevent dosing errors and adverse outcomes (4, 5, 7)

In our institution, it has been anecdotally observed that a patient's insulin requirements may be dramatically less upon admission to the hospital. To our knowledge, there is only one published study on U-500 insulin in hospitalized patients (8). Therefore, we sought to systematically investigate this observation in our facility.

Methods

Institutional Review Board (IRB) approval was obtained. We performed a retrospective chart review of patients treated with U-500 insulin as outpatients and admitted to the San Antonio Military Medical Center from July 2009 to July 2014. Inclusion criteria included patients between 18 and 89 years old with a hospital stay greater than 24 hours and treated with U-500 insulin at the time of admission. Patients were excluded if their home U-500 insulin dose was unable to be determined. Data collection included the outpatient total daily dose (TDD) of insulin, most recent glycosylated hemoglobin (HgA1c), age, height and weight. Once the patient was admitted, the TDD of insulin was recorded from the electronic medication administration record. Data collection began at midnight after the day of admission and hospital days were defined as the 24 hour period from midnight to midnight. Data was only collected on

as an outpatient require hospitalization, there are no formal guidelines or consensus among physicians on what insulin regimen or dose reduction should be used. Because of this lack of guidance, patients using U-500 insulin in our institution were prescribed a wide range of insulin regimens and starting doses. These patients routinely had their TDD of insulin reduced upon admission, although there was no reasoning given in the chart as to how the admitting team determined the starting inpatient insulin dose. We suspect that a large factor in the dose reduction came from physician unfamiliarity with U-500 insulin and uneasiness prescribing extremely high doses of insulin. On a survey of physicians and nurses performed at our institution, 47% of respondents reported being "very uncomfortable" with U-500 insulin use (9). We sought to evaluate and describe the inpatient insulin requirements in our hospital, so as to provide a framework for insulin regimen recommendations for future hospitalized U-500 patients and research studies.

All patients in this study received a lower TDD of insulin as an inpatient than as an outpatient with 89% of patients requiring ≤ 50% of their outpatient TDD. The dose reduction in these patients was even more striking knowing that hospitalized patients can have increased insulin requirements that include, but are not limited to, acute stress, parenteral and enteral nutrition, corticosteroid use and medical illnesses that contribute to hyperglycemia such as pancreatitis (1). Possible factors for decreased insulin requirements in these patients include controlled hospital diet, NPO status, and strict adherence to timing and dose of insulin injections by nursing staff. We suspect that the change in insulin requirement is predominantly driven by decreased in caloric intake as U-500 insulin patients tend to have obesity and patients in this study had an average BMI of38.9 kg/m^2. This is supported by a recent case report in which a patient on U-500 insulin had a large reduction in insulin after making dietary changes prior to bariatric surgery (10). The authors describe a patient on 320 units of U-500 insulin daily who was converted to U-100 detemir and lispro 10 days prior to surgery. The patient was instructed to dramatically reduce her caloric intake, and her glucose levels and insulin use were recorded. During the

final two days before surgery, the patient was on a clear liquid diet and discontinued all insulin injections. Blood glucose was consistently between 100-140 mg/dl during these two days when the patient was not injecting any insulin (10). Our study did not correct for potential causes of increased or decreased insulin requirements. Instead, it quantified the overall insulin requirements of U-500 patients after hospital admission.

To our knowledge, only one other study by Tripathy and Lansang has studied U-500 insulin in hospitalized patients (8). Their study was a retrospective chart review of 61 admitted patients who had been using U-500 insulin at home. They categorized the patients into two groups. One group continued U-500 insulin while in the hospital, and the other group was switched to U-100 insulin. The U-500 group remained on 85% of their home TDD (200 units TDD in hospital and 235 units TDD prior to hospitalization), but the group switched to U-100 only required 35% of their home TDD (35 units TDD in hospital and 100 units TDD prior to hospitalization). The average glucose between the two groups was not statistically significant (237.6 mg/dL for the U-500 group and 207.9 mg/dL for the U-100 group, $p = 0.480$). Their study also found a higher incidence of hypoglycemia in the U-500 group (8).

Our findings of U-500 insulin patients receiving 27% of their home TDD after being switched to a U-100 insulin regimen is similar to the Tripathy study group that was switched to a U-100 insulin regimen and received 35% of their home TDD. It is unclear why their group that continued on U-500 required 85% of their home TDD. One could speculate that perhaps they required more insulin because their home TDD was higher (235 units of insulin in the U-500 group versus 100 units insulin in the U-100 group) and were therefore more insulin resistant. However, the patients in our study had an average TDD of insulin of 337.6 units and received much less than 85% of their home TDD of insulin. While there are algorithms on converting U-100 insulin patients to U-500 insulin, there is a lack of information on converting U-500

insulin to U-100 insulin as an outpatient as well, so perhaps part of the difference could be due to the pharmacodynamics of U-500 insulin (10).

Limitations of this study include its small sample size, lack of hypoglycemia data due to only average daily glucose values being obtained, and the retrospective nature of the study. The average inpatient glucose of 234 mg/dl is above the American Diabetes Association (ADA) Standards of Medical Care in Diabetes goal of 140 to 180 mg/dL in hospitalized patients (11), so the patients in our study may have needed higher insulin doses than they received. However, the patients in our study had an average HgbA1c of 8.7% (corresponding to an outpatient eAG of 203.5 mg/dl) so they achieved clinically similar glycemic control while hospitalized on a much lower insulin dose. Also, on 35.1% of the hospital days, the average glucose was at the ADA recommended goal of less than 180 mg/dl while patients were receiving only 30.0% of their home TDD of insulin. In Figure 1, the change in the patients TDD of insulin and average glucose from baseline are graphed over the first five days of admission. It shows the glucose spikes on the first day with an average glucose of 242.5 mg/dl and patients receiving 24.5% of their home TDD of insulin. Over the following days, the amount of insulin increased as the insulin was titrated up and the glucose level slowly trended down. The amount of insulin received peaked at 36.2% of their home TDD on day four. By day five, the average glucose was lower than their outpatient eAG (195.8 mg/dl versus 203.5 mg/dl) and patients were on average receiving 29.2% of their home TDD of insulin.

U-500 insulin dosing is prone to errors on multiple levels in the hospital setting and many physicians are unfamiliar with its use, so conversion to U-100 insulin is a safer and preferred option. Despite a significant reduction in insulin TDD, the patients in our study had clinically similar glucose levels compared to their outpatient eAG. This study provides a general idea of insulin requirements in U-500 patients that are hospitalized and a starting point for future patients and studies. Since the average

inpatient TDD of insulin was 27% of their home TDD and 89% of admissions received ≤ 50% of their home TDD, we propose that it is reasonable to convert U-500 patients to U-100 insulin on admission with starting doses between 25% to 50% of their home TDD. The patient's outpatient glucose control, reason for admission, NPO status, admission glucose, and corticosteroid use should be taken into consideration by the admitting physician and the patients' glucose levels should be closely monitored and insulin titrated as needed to maintain adequate glucose control.

Conclusion

Patients taking U-500 insulin as an outpatient can be converted to a U-100 basal-bolus regimen at 25 to 50% of their home TDD upon hospital admission. Further prospective trial data is needed to best evaluate the ideal approach to this situation.

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Table 1
Patient Demographics, Insulin Doses and Glucose

	Total	Men	Women
Patients	27	19	8
Admissions	62	40	22

	Mean	Minimum	Maximum
Age (years)	64.4	47	85
BMI (kg/m^2)	38.9	26.4	54.7
HgbA1c (%)	8.7	5.7	15.5
Estimated Average Glucose (mg/dL)*	203.5	117	398
Outpatient TDD insulin (units of insulin)	337.6	100	1250
Length of Stay (days)	4.0	1	16
Average inpatient TDD Insulin (units of insulin)	91.0	8	400
Average inpatient BG (mg/dL)	234.4	97	450

Abbreviations: TDD, Total Daily Dose: BG, blood glucose: HgbA1c, glycated hemoglobin
*Calculated from HgbA1c

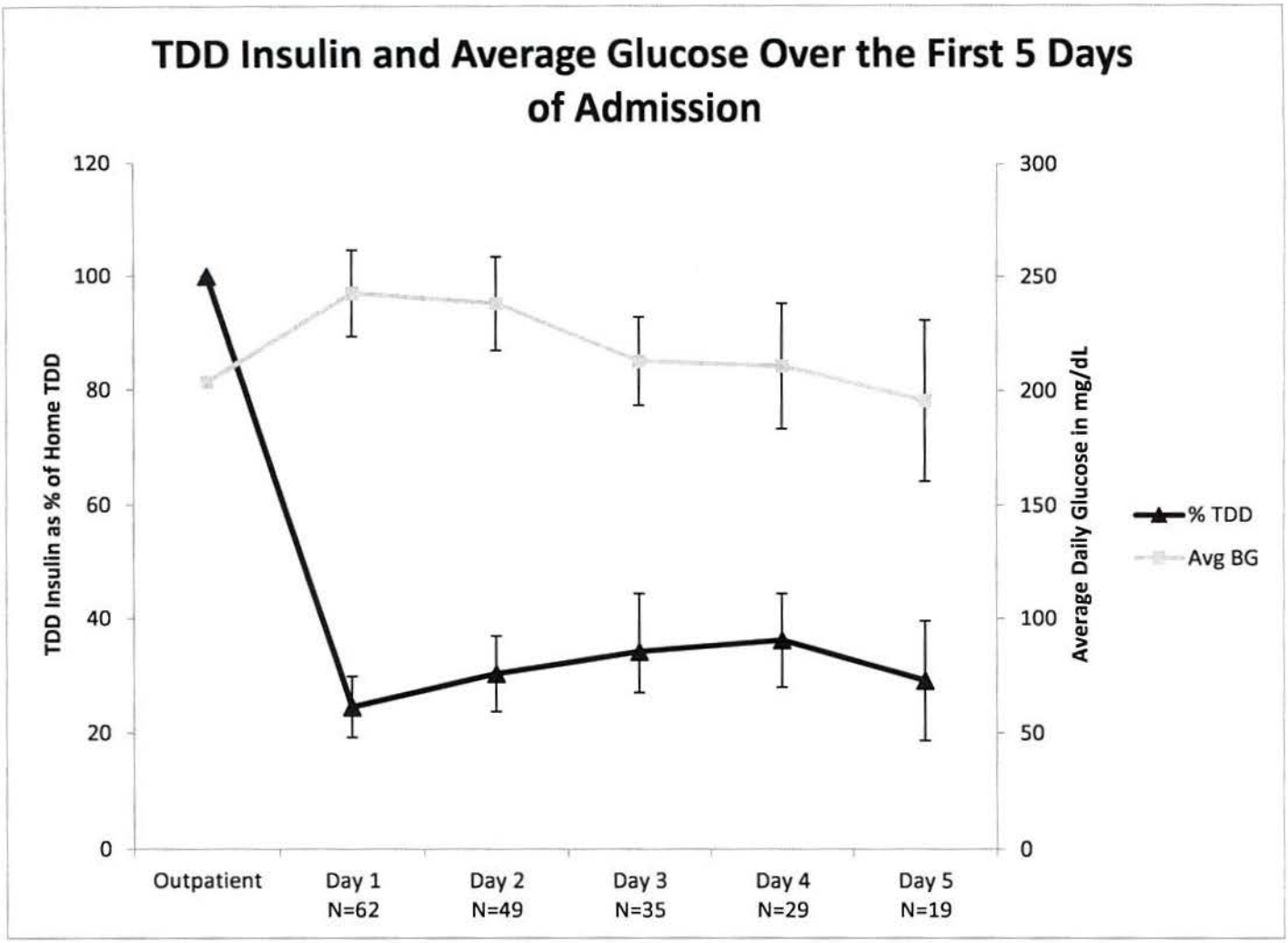

Figure 1: Outpatient total daily dose of insulin (TDD) and estimated average glucose (calculated from HgbA1c) compared to percent of home TDD of insulin and inpatient average blood glucose (BG) over the first five days of hospital admission.

Primer:	Name	Manufacture	Lot	Date Recd.
		Invitrogen		

0 *input nmoles of oligo
* must be > 100
0

Date Reconstituted

	tube 1			
100 µM	0			
vol in µL				

Primer:	Name	Manufacture	Lot	Date Recd.
	F HLAB e3	Invitrogen		5/?/2015

21.5 *input nmoles of oligo
* must be > 100
215

Date Reconstituted
27-Apr-16

	tube 1			
100 µM	215			
vol in µL				

Primer:	Name	Manufacture	Lot	Date Recd.
	R HLABe3	Invitrogen		5/?/2015

22 *input nmoles of oligo
* must be > 100
220

Date Reconstituted
27-Apr-16

	tube 1			
100 µM	220			
vol in µL				